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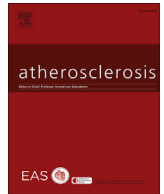
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Carotid plaque-thickness and common carotid IMT show additive value in cardiovascular risk prediction and reclassification



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ABSTRACT

Background and aims: Carotid plaque size and the mean common carotid intima-media thickness measured in plaque-free areas (PF CC-IMT_{mean}) have been identified as predictors of vascular events (VEs), but their complementarity in risk prediction and stratification is still unresolved. The aim of this study was to evaluate the independence of carotid plaque thickness and PF CC-IMT_{mean} in cardiovascular risk prediction and risk stratification.

Methods: The IMPROVE-study is a European cohort (n = 3703), where the thickness of the largest plaque detected in the whole carotid tree was indexed as cIMT_{max}. PF CC-IMT_{mean} was also assessed. Hazard Ratios (HR) comparing the top quartiles of cIMT_{max} and PF CC-IMT_{mean} versus their respective 1–3 quartiles were calculated using Cox regression.

Results: After a 36.2-month follow-up, there were 215 VEs (125 coronary, 73 cerebral and 17 peripheral). Both cIMT_{max} and PF CC-IMT_{mean} were mutually independent predictors of combined-VEs, after adjustment for center, age, sex, risk factors and pharmacological treatment [HR (95% CI) = 1.98 (1.47, 2.67) and 1.68 (1.23, 2.29), respectively]. Both variables were independent predictors of cerebrovascular events (ischemic stroke, transient ischemic attack), while only cIMT_{max} was an independent predictor of coronary events (myocardial infarction, sudden cardiac death, angina pectoris, angioplasty, coronary bypass grafting). In reclassification analyses, PF CC-IMT_{mean} significantly adds to a model including both Framingham Risk Factors and cIMT_{max} (Integrated Discrimination Improvement; IDI = 0.009; p = 0.0001) and vice-versa (IDI = 0.02; p < 0.0001).

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Conclusions: cIMT_{max} and PF CC- IMT_{mean} are independent predictors of VEs, and as such, they should be used as additive rather than alternative variables in models for cardiovascular risk prediction and reclassification.

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1. Introduction

The measurement of carotid plaque thickness, rather than the mean of common carotid intima-media thickness measured in plaque-free areas (PF CC- IMT_{mean}), is an important yet controversial issue for cardiovascular risk prediction and/or risk refinement. Both variables have been associated with vascular events (VEs), independently of conventional vascular risk factors (VRFs) [1]. However, the decision to use one or the other in models for risk prediction or risk stratification is often based on methodological issues such as accuracy and ease of measurement [2,3], or relative power in risk prediction [4–8]. Carotid plaque thickness and PF CC- IMT_{mean} are correlated, yet they differ considerably from a histological point of view and they can better be considered as distinct phenotypes [9] describing two different phenomena, being mainly due to atherosclerosis [10] and hypertrophy/hyperplasia of smooth muscle cells, respectively [2]. Several observational studies have focused on either carotid IMT (cIMT) or plaque, but few studies [5,8,11,12] have examined whether carotid plaque thickness and PF CC- IMT_{mean} can be used as additive rather than alternative variables in models for cardiovascular risk prediction and reclassification. With the aim of gaining further insight into this issue, we evaluated the independence of carotid plaque thickness (indexed in terms of cIMT_{max} i.e. the maximal carotid IMT detected in the whole carotid tree) and PF CC- IMT_{mean} , in cardiovascular risk prediction and/or risk refinement in a large, multicenter, prospective cohort study of high-risk individuals [Carotid Intima–Media Thickness (IMT) and IMT–Progression as Predictors of Vascular Events in a High–Risk European Population (acronym: IMPROVE)].

2. Patients and methods

2.1. Subjects

A complete description of the IMPROVE-study design, objectives, sampling strategy and methods for clinical and haematological evaluation has been reported in the text and Online Materials of Baldassarre et al. [13,14]. Briefly, a total of 3711 individuals (age 54–79 years) were recruited, with at least three VRFs but free of any cardio- or cerebro-VEs prior to enrolment. The participants were enrolled at 7 centers in 5 European countries: Finland (Kuopio, 2 centers), France (Paris), Italy (Milan and Perugia), The Netherlands (Groningen) and Sweden (Stockholm).

The occurrence of VEs (myocardial infarction (MI), sudden cardiac death, angina pectoris, ischemic stroke, transient ischemic attack, new diagnosis of intermittent claudication, or any surgical intervention or revascularization of coronary or peripheral arteries) was assessed at months 15 and 30 by regular visits, and at the end of follow-up (36 months in average) by phone interview. The sample size considered for this report is 3703 since the carotid walls were not properly visualized in 8 subjects.

2.2. Ultrasonographic assessment

The ultrasound procedure in the IMPROVE study has been described [13,14]. Briefly, 7 identical scanners (Technos System,

Esate, Genoa, Italy) equipped with 5–10 Mhz linear array probes were used and the images were recorded on sVHS videotapes by trained sonographers. The cIMT was measured centrally by trained readers at the ultrasound reading center in Milan. cIMT was assessed in the entire length of the common carotid, in the carotid artery bifurcation (1 cm proximal to the flow divider) and in the internal carotid artery (1 cm immediately distal to the flow divider) of both left and right carotids. At each of these segments, the mean and maximal values of IMT were measured on the far wall from three angles (anterior, lateral and posterior) by means of a specific software (M'Ath).

In this study, we also considered the mean of common carotid IMT measured in plaque-free areas (PF CC- IMT_{mean}), i.e. areas with a $\text{cIMT}_{\text{max}} < 1$ mm. This variable is the average of all plaque-free mean IMT values obtained from the left and right CC visualized in their entire length (excluding the 1st cm) with sequential 1 cm-long probe movements according to the 3 aforementioned scan angles. The total number of segments averaged for assessing PF CC- IMT_{mean} ranged from 6 to 24, according to the subject's neck length and according to the number of segments with $\text{cIMT}_{\text{max}} \geq 1$, which were excluded from the average calculation. The precision of cIMT_{max} has been reported [13]. Details on precision of PF CC- IMT_{mean} are provided in Supplementary Data.

2.3. Ethical considerations

The Ethics Committees of all participating institutions approved the IMPROVE study, which complied with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

2.4. Statistical analysis

Cox models were used to estimate crude and adjusted hazard ratios (HRs) and to compute adjusted Kaplan–Meier survival curves over 36 months of follow-up. The HRs comparing the top quartiles of cIMT_{max} (2.5 mm) and PF CC- IMT_{mean} (0.76 mm) to their respective 1–3 quartiles were calculated. We decided *a priori* to use these cut offs because the ASE consensus statement described PF CC- IMT_{mean} values \geq 75th percentile as indicative of increased cardiovascular risk [15]. Regarding plaques, we decided to use cIMT_{max} values \geq 75th percentile because most large longitudinal studies showed that the risk is mainly increased in the top quartiles or quintiles [16]. As a sensitivity analysis, we also tested models where cIMT_{max} and PF CC- IMT_{mean} were included as continuous variables. Cox models were stratified for center (Model-1), then further adjusted for age and sex (Model-2) and then for risk factors and pharmacological treatment (Model-3). Departure from the proportional hazard assumption was assessed by the Kolmogorov-type supremum test computed on 1000 Monte-Carlo simulations. Area under the ROC curves (AUC), Integrated Discrimination Improvement (IDI), and Net Reclassification Improvement (NRI) were used for assessing the potential of the PF CC- IMT_{mean} in improving risk prediction based on cIMT_{max} and risk factors included in the Framingham Risk Score (age, sex, total cholesterol, HDL-cholesterol, systolic blood pressure, diabetes, current smoking and antihypertensive treatments) and *vice-versa*. As in our previous

study [14], we included risk factors contained in the Framingham Risk Score as separated variables in all models, instead of the Framingham Risk Score, as this algorithm is not specifically calibrated for a European population. To assess the impact of $cIMT_{max}$ and PF CC- IMT_{mean} on the risk reclassification of subjects located in the so called “gray-zone” of risk prediction, we calculated the clinical NRI, i.e. the NRI only considering subjects at intermediate-risk ($10\% < \text{Framingham Risk Score} < 20\%$). Positive and negative predictive values (PPV and NPV) were also computed.

All statistical tests were two-sided at a level of significance of 0.05. All analyses were performed using the SAS statistical package v. 9.4 (SAS Institute Inc., Cary, NC, USA). Reclassification statistics were assessed with the SAS macros published by Cook and Ridker [17].

3. Results

The baseline characteristics of IMPROVE study participants were described [13,14]. Briefly, the mean age was 64.2 years and 47.9% of subjects were males. The participants were followed-up for a median of 36.2 months (interquartile range: 35.8 to 37.4) and 215 suffered a first VE, (incidence: 19.9/1000 person-years). Among these, 125 had a coronary event [34 had a MI (7 fatal), 3 suffered sudden cardiac death, 49 experienced symptoms of angina pectoris, 26 underwent angioplasty and 13 coronary bypass grafting]; 73 had a cerebrovascular event [32 had an ischemic stroke (0 fatal), 41 had a transient ischemic attack], and 17 had a peripheral VE (4 subjects underwent revascularization due to peripheral artery disease and 13 had a new diagnosis of intermittent claudication). Eighty participants had more than one VE during follow-up, but only the first event was used for the analysis of the primary combined endpoint.

3.1. $cIMT_{max}$, PF CC- IMT_{mean} and risk of combined VEs

In Cox regression models with mutual adjustment for $cIMT_{max}$ and PF CC- IMT_{mean} , both variables (top quartiles vs. quartiles 1–3) were significantly and independently associated with the risk of combined-VEs, after stratifying for center (Table 1, Model-1), as well as with further adjustment for age and sex (Model-2) and for risk factors and pharmacological treatment (Model-3). These results were virtually unchanged when $cIMT_{max}$ and PF CC- IMT_{mean} were analysed as continuous variables (data not shown). For both $cIMT_{max}$ and PF CC- IMT_{mean} , no significant departure from the assumption of proportionality of the hazards was observed ($p = 0.42$ and $p = 0.46$, respectively).

Fig. 1 shows the Kaplan-Meier incidence curves adjusted for Model-3 covariates and stratified into four groups according to $cIMT_{max}$ and PF CC- IMT_{mean} above or below their respective top quartiles (2.5 mm and 0.76 mm). The independent effect of the two variables is clearly shown.

Table 1 also shows that both $cIMT_{max}$ and PF CC- IMT_{mean} were independent predictors of cerebrovascular and coronary events in all models.

Supplemental Table 1 shows the same analyses as Table 1 restricted to “hard clinical events”. While no significant association with hard coronary events (myocardial infarction, sudden cardiac death) was detected, the measures of $cIMT_{max}$ and PF CC- IMT_{mean} remained significantly and independently associated with hard cerebrovascular events (ischemic strokes), even after adjusting for center, age, sex, Framingham risk factors (FRFs) and pharmacological treatments (Model 3).

3.2. Incremental predictive value of $cIMT_{max}$ and PF CC- IMT_{mean} in reclassification analysis

Table 2 shows the reclassification statistics for the combined

endpoints. In the first line, AUC, NRI and IDI values were obtained after adding PF CC- IMT_{mean} to a reference model that included FRFs and $cIMT_{max}$. In the second line, AUC, NRI and IDI values were obtained after adding $cIMT_{max}$ to a reference model that included FRFs and PF CC- IMT_{mean} . $cIMT_{max}$ appears to improve the classification of cases and controls more effectively than PF CC- IMT_{mean} (NRI: 8.2% vs. 2.4% and IDI: 0.02 vs. 0.009).

Supplemental Tables 2 and 3 and Table 3 show the estimated 10-year VE risk categories according to FRFs before and after adding $cIMT_{max}$ (Supplemental Table 2), PF CC- IMT_{mean} (Supplemental Table 3) and the combination of the two variables (Table 3). In Supplemental Table 2, the overall NRI was 10% ($p = 0.02$) and 32% of subjects at intermediate risk were reclassified. The addition of PF CC- IMT_{mean} to FRFs (Supplemental Table 3) resulted in the reclassification of only 23% of subjects at intermediate risk and the overall NRI was lower (5.3%) and not statistically significant ($p = 0.19$). However, when both variables were added (Table 3), the overall NRI increased to 13.9% ($p = 0.003$) and the percentage of subjects at intermediate-risk reclassified reached approximately 41%. Among these subjects, 30 cases and 425 non-cases were correctly reclassified, and 6 cases and 239 non-cases were wrongly reclassified, yielding a clinical NRI of 45.1%, compared to 29.6% using only $cIMT_{max}$ and 27.5% using only PF CC- IMT_{mean} .

PPVs and NPVs for those with a high Framingham risk score (FRS > 20) as well as for top quartile values of PF CC- IMT_{mean} , $cIMT_{max}$ or both, assessed considering combined-, coronary- or cerebrovascular events, are shown in Supplementary Fig. 1. As expected because of the low incidence of VEs (19.9/1000 person-years), the PPVs were rather low, (always < 21%). However, even the PPVs of the FRS, the most widely accepted predictor of VEs, were about half (9.5%, 3.6%, and 5.9% for combined-, coronary- or cerebrovascular events, respectively) of those obtained with the combination of PF CC- IMT_{mean} and $cIMT_{max}$ (18.5%, 7.9%, and 10.9%). The best PPVs were obtained when all three variables (FRS, PF CC- IMT_{mean} and $cIMT_{max}$) were in the high risk categories.

4. Discussion

This study shows that $cIMT_{max}$ (an index of the thickest plaque detected in the whole carotid tree) and PF CC- IMT_{mean} (an index of the common carotid background thickening) are both independent predictors of VEs, and that they independently add to risk reclassification in intermediate risk subjects. It is well known that, taken by themselves, carotid IMT and the presence/thickness of carotid plaques are both prognostic predictors of CV events, as reported by Naqvi and collaborators [1] in a “state-of-the-art” paper that examined many large cohort studies. Several studies have also investigated which of these two variables is the strongest predictor of VEs. Several meta-analyses [6,7] have unequivocally reported that plaques are more accurate in predicting VEs than CC-IMT. In addition, studies evaluating whether carotid ultrasonographic measurements provide additional prognostic information over and above VRFs have been strongly positive when based on carotid plaques, and/or on $cIMT$ variables incorporating plaques in their measurements [5,8,18–23], and weaker or even negative when based on $cIMT$ measured in plaque-free areas [5,8,16,20,21,23–26]. Hence, it is quite clear and widely accepted that if one must choose between CC-IMT measured in plaque-free areas or plaques (presence or thickness) for risk prediction and/or reclassification, the latter is the best choice.

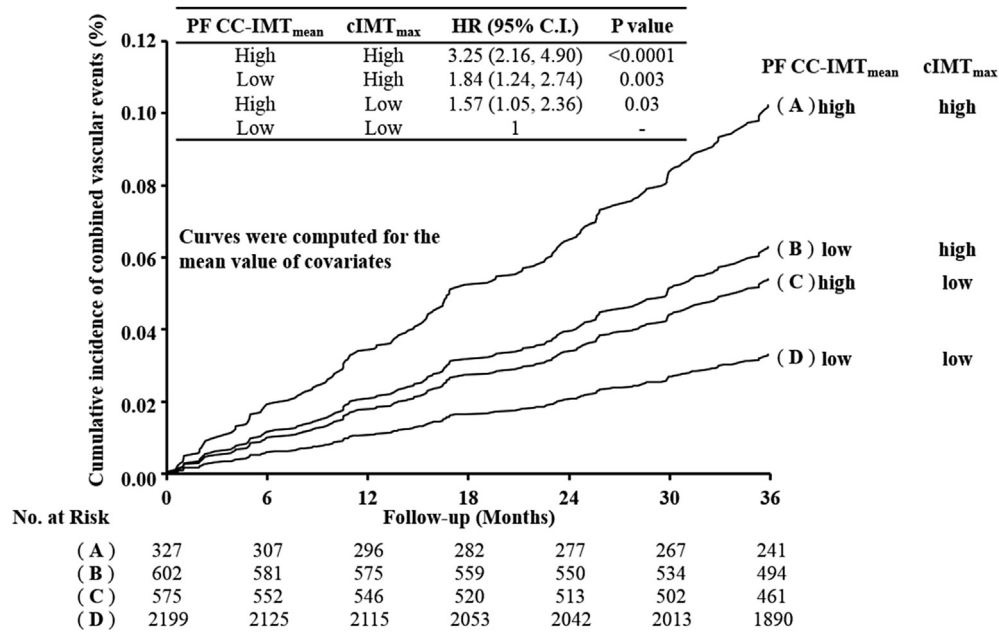
It is important to emphasise that, instead of assessing whether plaques or PF CC- IMT_{mean} are good and/or equipotent representations of the atherosclerotic process, the present study focuses on whether the two ultrasonographic measures represent complementary prognostic information when used together. To date, the

Table 1Hazard Ratios (95% CI) and *p* values of combined, cerebro- and cardio-vascular endpoints comparing top quartiles of both cIMT_{max} and PF CC-IMT_{mean} vs. quartiles 1–3.

	Model-1	Model-2	Model-3
Combined endpoints (n = 215)^a			
cIMT _{max}	2.05 (1.55, 2.72); <0.0001	1.88 (1.41, 2.51); <0.0001	1.98 (1.47, 2.67); <0.0001
PF CC-IMT _{mean}	1.89 (1.41, 2.53); <0.0001	1.69 (1.26, 2.27); 0.0005	1.68 (1.23, 2.29); 0.0011
Cerebrovascular endpoints (n = 73) (Ischemic stroke, transient ischemic attack)^a			
cIMT _{max}	2.7 (1.67, 4.36); 0.0001	2.55 (1.57, 4.14); 0.0002	2.76 (1.66, 4.6); 0.0001
PF CC-IMT _{mean}	2.25 (1.38, 3.68); 0.0012	2.07 (1.26, 3.4); 0.004	2.13 (1.26, 3.61); 0.005
Coronary endpoints (n = 125) (myocardial infarction, sudden cardiac death, angina pectoris, angioplasty, coronary bypass grafting)^a			
cIMT _{max}	1.69 (1.16, 2.47); 0.006	1.51 (1.03, 2.21); 0.036	1.58 (1.06, 2.37); 0.025
PF CC-IMT _{mean}	1.70 (1.15, 2.5); 0.007	1.47 (0.99, 2.17); 0.056	1.49 (0.99, 2.26); 0.057

Model-1: cIMT_{max} and PF CC-IMT_{mean} stratified by center; Model-2: as model-1 plus age and sex; Model-3: as model-2 plus Framingham risk factors, family history of diabetes, family history of hypertension, pack-years, and pharmacological treatments (statins, beta-blockers, ACE-inhibitors, diuretics and calcium-antagonists).

^a Among the 215 combined endpoints, 17 were peripheral VEs (4 subjects underwent revascularization due to peripheral artery disease and 13 had a new diagnosis of intermittent claudication) and, as such, included neither in the analysis on cerebrovascular endpoints nor in the one on coronary endpoints.

**Fig. 1.** Framingham risk factors-adjusted Kaplan-Meier incidence curves.

The study population was stratified according to cIMT_{max} and PF-CC-IMT_{mean} values above or below their respective 75th percentiles (2.5 and 0.76 mm), respectively. Curves were computed for the mean value of each covariate used in Table 1, Model-3 (i.e. center, age, sex, Framingham risk factors, family history of diabetes, family history of hypertension, pack-years and pharmacological treatments (statins, beta-blockers, ACE-inhibitors, diuretics and calcium-antagonists)). IMT, intima-media thickness; PF CC-IMT_{mean}, mean common carotid IMT measured in plaque-free areas; cIMT_{max}, measure of the thickest plaque detected in the whole carotid tree.

Table 2

Reclassification statistics for PF CC-IMT_{mean} above or below top quartile as compared to classification based on Framingham Risk Factors (FRFs) and cIMT_{max} and vice-versa in risk models with combined vascular endpoints.

New model	Reference model	AUC ref. model	AUC new model	<i>p</i> value	NRI (95% CI)	<i>p</i> value	IDI (99% CI)	<i>p</i> value
FRFs + cIMT _{max} + PF CC-IMT _{mean}	FRFs + cIMT _{max}	0.661	0.671	0.15	2.4% (-3.5, 8.3)	0.42	0.009 (0.003, 0.016)	0.0004
FRFs + PF CC-IMT _{mean} + cIMT _{max}	FRFs + PF CC-IMT _{mean}	0.657	0.671	0.054	8.2% (0.1, 16.3)	0.047	0.02 (0.010, 0.029)	<0.0001

When NRI and/or IDI values are positive with a *p* < 0.01, the new model is better than the reference model, which includes FRFs and cIMT_{max} and vice-versa. AUC, area under the ROC curve.

potential complementarity of plaque and cIMT in risk prediction and reclassification has been addressed in only four large prospective cohort studies [5,8,11,12], but with conflicting results. While Plichart [5] and Gardin [12] showed that adding plaques to cIMT does not result in a statistically significant improvement in risk prediction, Nambi [11] and Gepner [8], in agreement with our data, found that the prediction of coronary artery disease improves when cIMT and plaques are combined, compared with each

measurement alone.

Some methodological differences in plaque definition and targets/modality of carotid IMT measurements between our study and the studies mentioned above should be mentioned. In the study of Plichart [5] and Gepner [8], plaques were defined as localized echo-structures for which the wall thickening was at least 50% greater than surrounding vessel walls. Thus, even a lesion with a thickness <1 mm was considered as “plaque” if the thickness of surrounding

Table 3
Risk reclassification comparing the extrapolated 10-years risk according to Framingham Risk factors (FRFs) before and after adding both cIMT_{max} and PF CC-IMT_{mean} in the prediction of combined vascular events.

10-year risk categories for FRFs	10-year risk categories for FRFs plus cIMT _{max} plus PF CC-IMT _{mean}			N (%) reclassified
	<10%	10–20%	>20%	
<10%				
N = 678 (20%)	556 (82%)	113 (16.7%)	9 (1.3%)	122 (18%)
Observed-risk (95% C.I.)	6.4 (3.2, 10.8)	11.6 (3.2, 25.4)	No events	
10–20%				
N = 1715 (52%)	431 (25.1%)	1015 (59.2%)	269 (15.7%)	700 (41%)
Observed-risk (95% C.I.)	4.5 (1.7, 8.8)	11.1 (7.7, 15)	38 (25.6, 52.7)	
>20%				
N = 920 (28%)	0 (0%)	322 (35%)	598 (65%)	322 (35%)
Observed-risk (95% C.I.)		24.2 (15.5, 34.7)	36.7 (28.4, 46)	
NRI: 13.9%; $p = 0.003^a$				
Clinical NRI 45.1%; $p < 0.0001^b$				

^a NRI: 11.0% (3.1, 18.9); $p = 0.007$; when statins are added to FRFs.

^b Clinical NRI: 26.7% (13.0, 40.3); $p = 0.0001$; when statins are added to FRFs.

walls was <0.5 mm. By contrast, in our study, we used as cut-off the top quartile of cIMT_{max} (2.5 mm), so only real atherosclerotic plaques were considered. The other two studies [11,12] evaluated the utility of adding a measure of plaque burden to cIMT variables which neither focused strictly on the common carotid artery nor on plaque-free areas. For example, the cIMT variable used in Gardin's analysis [12] was the mean of maximum IMT measurements of several carotid segments (which we define as IMT_{mean-max}), a variable whose values are directly affected by the presence/absence of plaques. A similar comparison previously performed in the IMPROVE cohort [14] produced similar results by showing that the presence/absence of plaque did not add to reclassification when used on top of ultrasonographic variables which incorporate plaques, yet added to reclassification when combined with variables measured in plaque-free areas. Moreover, our data also show that the NRI and IDI, provided by the combination of the two variables used on top of FRFs, are not inferior to those obtained by using IMT_{mean-max} on top of FRFs (Supplemental Table 4). These data agree with another study of Nambi et al. [27], who showed that the evaluation of the carotid artery for plaque presence and measurement of CC-IMT (which is easier and more precise than considering IMT_{mean} or IMT_{mean-max} in the whole carotid tree) provide a good alternative to the measurement of cIMT in all segments of the carotid tree for risk prediction and reclassification.

In this study, we, for three reasons, decided *a priori* to analyse the complementarity of cIMT_{max} and PF CC-IMT_{mean}: (1) literature indications according to published data [15,16], (2) these are the two variables most frequently used in clinical settings, and (3) there is evidence that, when taken by themselves, measurements of both variables can be performed in a reproducible way in the clinical setting [28,29].

Our results distinctly support the concept that these two measures are complementary in risk prediction. Indeed, at the end of the follow-up period, FRF-adjusted Kaplan Meier curves (Fig. 1) shows a substantial increase of event risk in the stratum where both cIMT_{max} and PF CC-IMT_{mean} indicate the presence of sub-clinical disease, compared with the strata where only one of the two variables were in the top quartile range.

When Cox analyses were restricted to cerebrovascular or coronary endpoints (regardless of whether “hard” or not), the strength of association between top quartile values and risk of disease was always greater with cerebrovascular than with coronary endpoints, and this was true even after the analyses were adjusted for center, pharmacological treatments and FRFs. A potential explanation is that FRFs are predominantly a tool for prediction of coronary events [30], whereas cerebrovascular events are related to a broader array

of causes [31], including embolism from cardiac arrhythmias and/or valvular disease or hypertension giving rise to small vessel disease [32]. Another possible explanation is that the presence of atherosclerosis in the carotid arteries is both a marker and a cause of cerebrovascular events, whereas it is merely a marker of coronary events.

The complementarity of cIMT_{max} and PF CC-IMT_{mean} is confirmed by the reclassification analysis, particularly in the intermediate-risk category. With such analysis, several authors have reported that the improvement of risk stratification over traditional VRFs provided by PF CC-IMT_{mean} alone [5,20,21,24,25] is less consistent than that provided by plaques alone [5,18–22]. As well as confirming this finding (Supplemental Tables 2 and 3), we show here a substantial improvement of risk stratification over FRFs when both cIMT_{max} and PF CC-IMT_{mean} are used (Table 3), with a 3.9% (13.9% minus 10%) increase of NRI and a 15.5% (45.1% minus 29.6%) increase of clinical NRI when compared with the model including FRFs and cIMT_{max} (Supplemental Table 2). Specifically, Table 3 shows that the observed risk (38%; 95% CI 25.6, 52.7) of individuals reclassified to a higher risk category was actually much higher than the threshold of 20% estimated by FRFs only, and that the observed risk of individuals reclassified to a lower risk category was actually much lower (4.5%; 95% CI 1.7, 8.8) than the original 10–20% risk estimated by FRFs. By contrast, Table 3 shows that reclassification of subjects originally classified by FRFs at low or at high risk has to be viewed as inappropriate. For example, individuals who moved from the high-to intermediate-risk category had an observed risk of 24.2% (95% CI 15.5, 34.7), i.e. a risk greater than the threshold of 20%.

Despite this, at least in the intermediate-risk category, the benefits gained from the improvement in risk classification seem to easily offset the negligible additional costs required for measuring not only cIMT_{max} but also CC-IMT in plaque-free areas. Supporting the results obtained with Cox and reclassification analyses, when the two ultrasonographic variables were both in the top quartile, the improvements over the best performing single variable were consistent (+36%, +27% and +40% for composite, cerebrovascular and coronary-endpoints, respectively). Of note, the PPVs considering the single ultrasonographic variables were higher than the PPV of the FRS>20 and the addition of FRS>20 to the test with both the ultrasonographic variables in the top quartile resulted in a minor PPV improvement (ranging from 6 to 11%).

Another evidence supporting measurement of PF CC-IMT_{mean} comes from 1) studies showing that the incidence of stroke [33] and coronary events [34] is related to cIMT even in the absence of plaques, 2) case-control studies showing that it is preferable to

combine carotid IMT measurement with plaque assessment rather than using either measurement alone as screening tests for CHD [35], and 3) studies showing that the associations between cIMT and stroke remained significant even after adjusting for the presence of carotid plaques [33]. Moreover, a meta-analysis including eight relevant studies with cIMT assessment showed that for each 0.10 mm increase in CC-IMT, the estimated incidence of MI increases by 5% (from 12 to 17%) [36], thus suggesting that, even when measured in plaque-free areas, CC-IMT measurements still contain additional information for risk prediction regardless of the presence or absence of atherosclerotic plaques.

The complementary prognostic value of cIMT_{max} and PF CC-IMT_{mean} has scientific support also from a biological/pathophysiological perspective. Carotid IMT_{max} is a plaque marker [23] and reflects a focal phenomenon mainly related to atherosclerotic processes such as inflammation, oxidation, endothelial dysfunction, foam cell proliferation and/or thrombosis [10,37]. PF CC-IMT_{mean}, instead, mainly reflects diffuse, non-atherosclerotic, adaptive changes to increased shear stress mediated by aging [37] or hypertension [2,38]. In addition, variants in genes involved in pathways leading to atherosclerosis (e.g. inflammation, oxidative stress, and diabetes) were differentially associated with the two variables [9,39–43]. Taken together, these pieces of evidences support the concept that, even if the processes underlying cIMT_{max} and PF CC-IMT_{mean} formation may share some common mechanisms for initiation and progression [9,37,44], the two phenotypes represent biologically distinct aspects - or stages - of atherosclerosis [45]. Their overlap is only partial [37] and, consequently, they have different, independent and complementary prognostic value [2,11,19,36,46].

4.1. Strengths and limitations

The study has several strengths. Firstly, this is the first report evaluating the complementarity of cIMT_{max} and PF CC-IMT_{mean}, in terms of prediction and reclassification, in European subjects at high risk of cardiovascular disease. The second strength is the tight control of the methodology for carotid image acquisition and measurement of ultrasonographic variables. Thirdly, all sonographers involved in the study were trained and certified, and all scans were read blindly in the same reading center. Other advantages are the large sample size and the tight standardizations of all methods across all recruitment units. There are also potential limitations: firstly, extrapolation of the findings to the general European population or to patients with fewer than 3 VRFs should be done with caution. However, the HRs observed are similar to those reported in other large population studies [1]. Secondly, the low number of VEs restricted the precision of estimates especially in subgroup analyses (coronary and cerebrovascular events). Thirdly, a further stratification according to number of plaques (i.e. number of segments with a cIMT_{max} > 1 mm), as recently suggested [35], was not considered because of the limited number of VEs, and because almost all subjects (92.1%) in our “high risk” population have more than two plaques. However, repeating the analysis shown in Table 1 (Model 3) after including the number of plaques among covariates did not change the results substantially (data not shown). Fourthly, the prevalence of subjects treated with statins (40%) may have affected our reclassification analyses. It should be emphasized, however, that results did not change when statins were added to the FRFs (see footnotes of Supplemental Tables 2 and 3 and Table 3) or when the analysis was limited to statin-naïve individuals. In the latter case, for example, compared with a model including FRFs only, the IDI values of models including “FRFs + cIMT_{max}” or “FRFs + PF CC-IMT_{mean}” or their combination (FRFs + cIMT_{max} + PF CC-IMT_{mean}) were 0.014 (95% CI 0.005, 0.024), $p < 0.0001$; 0.008

(95% CI 0.001, 0.015), $p = 0.005$; and 0.019 (95% CI 0.008, 0.030), $p < 0.0001$, respectively.

We are aware that, based on concerns about quality of cIMT measurements and on the results of three review/meta-analyses [47–49], the working group on the 2013 ACC/AHA Cardiovascular Risk Guidelines [50] decided to advise against measuring cIMT in routine clinical practice for risk assessment for a first cardiovascular event in the general population. Nonetheless, our study has shown that cIMT_{max} and PF CC-IMT_{mean} contribute significant and independent incremental prediction beyond FRFs alone, and that it is better to combine than use either measure alone.

4.2. Conclusions

Bearing in mind the almost negligible costs required for adding measurements of PF CC-IMT_{mean} in scans devoted to cIMT_{max} measurements, we conclude that a risk stratification strategy based on the concomitant measurement of cIMT_{max} and PF CC-IMT_{mean}, as an adjunct to FRFs, is a rational approach for better identifying subjects who need to be treated with pharmacological and/or lifestyle intervention (diet, smoking cessation etc.).

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2017.05.023>.

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